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COMPLETE SPECIFICATION

Sterilisation of Solids for use in Aqueous Suspensions

We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the processing of medicinals. More particularly, it relates to the sterilization of water-insoluble solid medicinals for incorporation into sterile aqueous suspensions suitable for parenteral or ophthalmic use.

Solid medicinals for use in aqueous suspensions are customarily sterilized in several ways, such as by exposure to gases, for example, ethylene oxide; by use of chemical sterilizing agents added directly to the aqueous suspension, such as liquid propylene oxide, betapropiolactone, or diethyl pyrocarbonate; and by dry heat sterilization. Certain hazards and disadvantages are characteristic of these known sterilizing processes. For example, many sterilizing agents effect sterility by alkylation, and it is known that alkylating agents are also carcinogens. Furthermore, certain sterilizing agents produce toxic end products or contaminants such as residual sterilizing agents and/or ethylene glycol or ethyl alcohol. Moreover, sterilizing agents such as betapropiolactone hydrolyse into acidic end products. Similarly, gases such as ethylene oxide may be explosive and trace amounts of moisture have been known to inactivate both betapropiolactone and diethyl pyrocarbonate with no apparent physical change of the formulation noted. Also, dry heat sterilization discolors or destroys certain solids even at temperatures below 120°C. For instance, the steroid, dexamethasone acetate, turns a brownish-yellow at 100°C. dry heat temperature. Finally, the known sterilization processes and techniques involved in aseptic crystallization and recrystallization of sterile solids within definite particle size ranges involve aseptic intrusions for sampling, sub-division, packaging and storage under sterile conditions.

This invention seeks to eliminate the prior complex and expensive processes and techniques involved in aeptic crystallization and recrystallization of sterile solids within predetermined particle size ranges, and to eliminate the problems attendant to the sampling, subdividing packaging and storage of a sterile solid medicinal.

In addition, this invention seeks to eliminate the need for adding a separate chemical agent for the purpose of sterilizing solid medicinals, and to eliminate the problem of affecting the pH of a sterile suspension by the sterilization procedure.

This invention provides a process for sterilizing particulate substantially water-insoluble solid medicinal material which comprises suspending the particulate solid medicinal material in a saturated aqueous solution of sodium chloride containing an excess of undissolved sodium chloride, heating the saturated sodium chloride solution containing the particulate medicinal material and excess of sodium chloride to an elevated temperature above 100°C, maintaining said elevated temperature until sterilization is effected, and then allowing the sterilized product to cool, the excess of sodium chloride being sufficient to maintain a saturated solution of it at the said elevated temperature. Preferably a 10% excess of sodium chloride above the concentration necessary to form a saturated solution at 100°C is incorporated and a wetting agent is added to facilitate wetting of micro-fine powders. The concentrations of sodium chloride and medicament employed may be such that on dilution to give a suitable concentration of medicament the formulations fall within the isotonic range. Compositions of this invention may contain sodium bisulfite.

Preferably the sterilization according to the process of this invention is carried out at ele-

vated pressure, particularly at a temperature of from 110° to 130°C.

The water-insoluble medicinal substances for suspension may be prereduced to appropriate particle size by chemical or physical methods, such as crystallization, milling by ball or other mechanical means, or by the air attrition methods of jetomizing or microatomizing.

Although the solubility in water of certain solid medicinals, which may be non-electrolyte salts or salt formers, intended for aqueous suspension may be practically negligible, the rate of solution and solubility of the majority of these solids increase in proportion to the elevation in temperature, such as that necessary for sterilization processes, i.e. from room temperature (20—30°C) to elevated temperatures, including autoclaving temperatures (110—130°C). Upon re-cooling the system to 20—30°C, those solids that dissolve and redissolve at temperatures above 100°C are frequently recrystallized with incident growth into different sizes and forms not acceptable for suspension purposes, for one reason or another.

Generally, the theory of the process of this invention is that the solubility of non-electrolytes such as these solid medicinals intended for suspension in water is decreased by the presence of the electrolyte sodium chloride. The sodium chloride forms a solution of ions which require water for their hydration; thus in a saturated solution of sodium chloride there is little or no water available for solution of the non-electrolyte solid. Ideally, the solubility of sodium chloride in water is affected by less than 10% by variation in temperature. The addition of sodium chloride in concentration sufficient to form saturated solutions at both room and elevated temperations, plus a 10% excess, prevents the solution of the solids at the elevated temperatures, thus eliminating changes in crystal size and form upon subsequent cooling.

While this invention has been found to be particularly useful in the preparation of aqueous suspensions of insoluble steroids, e.g. dexamethasone and its derivatives suitable for parenteral and ophthalmic use, non-steroidal substances have also been sterilized by use of this process. The folowing Examples 2—16 illustrate the process of this invention, while Example 1 is included for comparison.

EXAMPLE 1

An attempt to formulate an aqueous suspension for parenteral use of dexamethasone acetate by the heretofore utilized methods resulted in the formation of needle-shaped crystals which were difficult or impossible to formulate. Caking and coating of the aseptic vials resulted. An attempted dry heat sterilization even at temperatures in the 100—120°C. range resulted in discoloration of the dexamethasone acetate. Sterilization by exposure to ethylene oxide gas was avoided because of potential ethylene glycol contamination of a substance for parenteral administration. Lyophilization of a solution of dexamethasone acetate from a dioxane solution (sterile) and aseptic glass bead milling for particle size reduction resulted in a change in crystal form and a particle size distribution indicating the presence of glass particles. Dexamethasone acetate jetomized to a particle size distribution of 90% below 10 microns and sterilized by autoclaving resulted in the growth of crystal sizes to 300 to 400 microns. Addition of salt such as sodium citrate, sodium acid phosphate, or concentrations of sodium chloride below the saturation level, resulted in a similar crystal size growth.

EXAMPLE 2

An aqueous suspension suitable for parenteral administration and having the following composition is as follows:

Dexamethasone acetate	8 m.g. as alcohol
Sodium chloride	8 m.g.
*Wetting agent	0.75 m.g.
Benzyl alcohol	9 m.g.
Sodium carboxymethyl-cellulose (LV)	5 m.g.
Water for injection	q.s. ad 1 ml.

Step A

The 0.8 parts of sodium chloride are added to 1.6 parts of water for injection hereinafter designated as water. Complete solution of the sodium chloride does not occur even with the application of heat to the boiling point. The mixture is cooled to 80—90°C. or any temperature down to room temperature. The dexamethasone acetate in a jetomized form is added and watted. The ease of wetting the microfine solid may be increased by the addition of an increment such as 10% of the formulated quantity of the wetting agent. The system is sterilized by autoclaving at 121°C. for 20—30 minutes.

Step B

The balance of the wetting agent and sodium carboxymethylcellulose are dissolved in 70 parts of water. The benzyl alcohol is added and dissolved. This solution is clarified by filtration such as through a sintered glass filter, and then sterilized by autoclaving at 121°C. time at temperature, for a minimum of 15 minutes.

*The actual wetting agent used throughout these examples is polyoxyethylene (20) sorbitan monooleate, a complex mixture of polyoxyethylene ethers of mixed partial oleic esters of sorbitol anhydrides. d. 1.06—1.10, viscosity 270—430 centistokes.

Step C

The resultant product of Step A is combined with the resultant product of Step B aseptically and sterile water is added aseptically to 100 parts. The system is homogenized aseptically and divided under sterile conditions into ampules or multidose vials.

The dexamethasone acetate contained in the sterile suspension prepared in accordance with this method showed no crystal size growth. X-ray analysis indicated no change in crystal form. Analytical studies, including infra-red analysis, indicated no decomposition of the dexamethasone acetate even after autoclaving the steroid-sodium chloride mixture for one hour at 121°C.

EXAMPLE 3

An aqueous suspension suitable for parenteral administration is prepared according to the method and composition of Example 2, but replacing the sodium carboxymethylcellulose (LV) with 50% sorbitol solution.

EXAMPLE 4

An aqueous suspension suitable for parenteral administration and having a composition similar to those of Examples 2 and 3, but containing 2 mg. dexamethasone alcohol per ml. represented as dexamethasone acetate, is prepared using the method of Example 2.

EXAMPLE 5

An aqueous suspension suitable for parenteral use and having the following composition and prepared in a manner similar to Example 2 is as follows:

Dexamethasone acetate	8 mg. as alcohol
Dexamethasone phosphate	2 mg. as alcohol
Benzyl alcohol	9 mg.
Sodium chloride	6.67 mg.
Sodium carboxymethyl-cellulose (LV)	5 mg.
Creatinine	5 mg.
Wetting agent	0.75 mg.
Sodium bisulfite	1.0 mg.
EDTA disodium	0.5 mg.
Sodium hydroxide	q.s. pH 6.8
Water for injection	q.s. ad 1 ml.

Step A

The 0.667 parts of sodium chloride are added to 1.5 parts water, then the procedure of Example 2, Part A is followed.

Step B

The sodium carboxymethylcellulose (LV) is dissolved in 40 parts of the water, clarified by filtration, sterilized by autoclaving at least 15 minutes time at a temperature of 121°C.

Step C

The balance of the ingredients are dissolved in 40 parts of water and this solution is sterilized by filtration through a sterlizing filter.

Step D

The product of Step A is combined with the product of Step B, and this then with the product of Step C. Then sterile water is added to make 100 parts. The suspension is circulated through a homogenizer at 1500—3000 psi, then collected in a sterile receiving vessel suitable for aseptic sub-division of a suspension. The suspension is then subdivided aseptically.

The chemical stability and physical stability of this suspension has been observed over a period of one year. Chemical assays were above 100% of that of the label claim after one year. The particle size was measured microscopically using a graduated micron scale, and particle size distribution curves were obtained using a Coulter counter. Microscopically, little to no growth was observed of crystal size after one year at room temperature. However, some crystal growth was noted in the 37°C. and 50°C. storage temperature samples even after three to six months storage. At the elevated temperatures, the increased solution of dexamethasone acetate results in growth to crystal sizes up to a maximum of 50—60 microns at 50°C. Particle size distribution curves after one year at room temperature measured by the Coulter counter yielded results of 90% below 18 microns and 0% above 28 microns. The particles in this suspension are flocculated and the Coulter counter does not differentiate between single particles and flocs. The initial Coulter counter curve had shown 90% below 17 microns, none above 25 microns.

EXAMPLE 6

An aqueous suspension suitable for parenteral administration and having a similar composition as that of the product of Example 5 is prepared according to the method of that Example by increasing the dexamethasone alcohol content to 18 mg. alcohol per ml. added as dexamethasone acetate. In this case the concentration of wetting agent is increased to 2 mg. per ml. This suspension has been prepared using both autoclaved and non-autoclaved dexamethasone acetate. The autoclaved dexamethasone acetate in suspension contains 90% of its particles below 13.5 microns whereas the non-autoclaved steroid in suspension measured 90% below 11.5 microns. Neither of the two suspensions had particles above 30 microns. The jetomized steroid prior to formulation of both the autoclaved and the non-autoclaved compounds contained particles 90% below 10 microns for the former, and 90% below 8.5 microns for the latter. A similar small increase in particle size resulted in both suspensions containing either autoclaved or non-autoclaved steroids immediately upon formulation as measured by the Coulter

counter and indicates the measurement of not only individual crystals but flocs of crystals of the lower particle sizes. The suspension containing the non-autoclaved dexamethasone acetate was not sterile, however.

EXAMPLE 7

An aqueous suspension suitable for parenteral use and having a similar composition as that of Example 5, but containing 2 mg. alcohol per ml. added as dexamethasone acetate is prepared according to the method of that Example, and reducing the concentration of wetting agent to 0.375 mg. per ml.

EXAMPLE 8

An aqueous suspension suitable for parenteral use and having a similar composition to that of the products of Examples 5, 6, and 7, but containing 50% sorbitol in place of the sodium carboxymethylcellulose (LV) is prepared according to the method of Example 6.

EXAMPLE 9

An aqueous suspension suitable for parenteral use containing lidocaine hydrochloride may be prepared having the following composition:

Dexamethasone acetate	8 mg. alcohol
Dexamethasone phosphate	2 mg. alcohol
Lidocaine hydrochloride	10 mg.
Sodium bisulfite	1 mg.
EDTA disodium	0.5 mg.
Creatinine	5.0 mg.
Wetting agent	2.0 mg.
Sodium carboxymethylcellulose (LV)	5.0 mg.
Benzyl alcohol	9.0 mg.
Sodium chloride	6.67 mg.
Sodium hydroxide	q. s. pH 6.8
Water for injection	q. s. ad 1 ml.

This composition may be prepared in accordance with the procedure set forth in Example 5, however, the lidocaine hydrochloride can be added as either the base converted to the hydrochloride prior to the addition using hydrochloric acid or as the hydrochloride salt. The pH of the suspension is adjusted to 6.80 to maintain solution of the lidocaine, and for optimum steroid phosphate stability. The solution of the lidocaine hydrochloride is added to the product of Step C prior to sterilization by filtration.

EXAMPLE 10

A sterile aqueous suspension suitable for ophthalmic use and having the following composition is as follows:

	mg. per ml.
Hydrocortisone alcohol microcrystalline—90% below 10 microns	10
Sodium chloride	8.0
Phenylethyl alcohol	5.0
Wetting agent	2.0
EDTA disodium	0.5
Sodium carboxymethylcellulose (LV)	5.0
Water for injection	q. s. ad 1.0 ml.

Step A

The sodium chloride 0.8 parts is added to 1.8 parts of water for injection. Then the procedure is identical to Example 2, Part A, except that the hydrocortisone compound is added in place of the dexamethasone.

Step B

Identical to Example 2, Step B.

Step C

Identical to Example 2, Step C.

Step D

Identical to Example 2, Step D, except that the product is sub-divided into sterile glass or plastic containers suitable for ophthalmic use. This product has shown excellent physical and chemical stability properties over a period of six months.

EXAMPLE 11

An aqueous suspension suitable for parenteral use containing prednisolone tertiary butyl acetate is as follows:

	mg. per ml.
prednisolone tertiary butyl acetate (microcrystalline) 90% below 10 microns	20 mg.
Benzyl alcohol	9 mg.
Sodium chloride	8 mg.
Sodium carboxymethylcellulose (LV)	5 mg.
Wetting agent	2 mg.
Water for injection	q. s. ad 1 ml.

Prepared in the same manner as Example 2.

Other steroids, betamethasone acetate, triamcinolone acetonide, and methyl prednisolone acetate have been sterilized using this invention. When using conventional methods of steam sterilization, betamethasone acetate was observed and crystal size showed growth from maxima of 70 micron needles to 400—500 micron long needles, which are not suitable for parenteral use.

Non-steroid substances have also been sterilized using this invention for both ophthalmic and parenteral use.

EXAMPLE 12

An aqueous suspension of a non-steroidal anti-inflammatory agent (indomethacin) suitable for parenteral administration, particularly for IM or IA injection, and having the following composition has been prepared:

	mg. per ml.
Indomethacin	50 mg.
Lecithin	1 mg.
Benzyl alcohol	9 mg.
Wetting agent	2 mg.
Sodium chloride	8 mg.
EDTA disodium	0.5 mg.
Sodium bisulfite	1 mg.
Sodium carboxymethylcellulose (LV)	5 mg.
Sodium hydroxide	q. s. pH 5—6
Water for injection	q. s. ad 1 ml.

Step A

The indomethacin is sterilized in a manner identical to that of Example 2, Step A, except that one-half of the formulated amount of sodium bisulfite is included here.

Step B

The lecithin is dissolved in 10 parts of water, clarified by filtration through a coarse sintered glass filter, and sterilized by autoclaving at 121°C. for 15 minutes.

Step C

The sodium carboxymethylcellulose (LV) is prepared in the manner identical to that of Example 5, Step B, except that only 30 parts of water are used.

Step D

The balance of ingredients are prepared in the same manner as in Example 5, Step C.

Step E

Upon cooling to room temperature, the product of Step B is added to the product of Step A and the mixture agitated for 15 minutes, and then added to the combination of the product of Step C and Step D, whereupon the formula is brought to volume with water and agitated for one-half hour. The resulting suspension is homogenized as in the previous examples and sub-divided into containers suitable for parenteral use.

EXAMPLE 13

Compositions are prepared in a corresponding manner to those of Examples 11 and 12 but with a 50% sorbitol solution in place of the sodium carboxymethylcellulose.

EXAMPLE 14

An ophthalmic suspension of indomethacin, prepared in accordance with Example 12, is as follows:

	mg. per ml.
Indomethacin jetomized	10 mg.
Lecithin	0.2 mg.
EDTA disodium	0.5 mg.
Sodium chloride	6.67 mg.
Sodium citrate	1.8 mg.
Citric acid	0.2 mg.
Phenylethyl alcohol	5.0 mg.
Wetting agent	2.0 mg.
Sorbitol solution	10.0 mg.
Water for injection	q. s. ad 1 ml.

EXAMPLE 15

Compositions according to Examples 12 and 14 are correspondingly prepared, but with concentrations of indomethacin of 5—50 mg. per ml; the concentration of lecithin is kept proportional to the concentration of indomethacin, i.e., 0.4 mg. lecithin to each 20 mg. indomethacin.

EXAMPLE 16

An ophthalmic suspension of thiabendazole, an antifungal agent, may be prepared in a manner identical to that of Example 5, and has the following composition:

	mg. per ml.
Thiabendazole jetomized	40 mg.
Phenylethyl alcohol	5 mg.
Benzalkonium chloride	0.2 mg.
Sorbitol solution	10 mg.
Hydroxyethylcellulose	1 mg.
EDTA disodium	0.5 mg.
Sodium chloride	8.0 mg.
Water for injection	q. s. ad 1 ml.

In this composition the hydroxyethylcellulose replaces the sodium carboxymethylcellulose of the former example.

There are many advantages incident to the use of the process of this invention. Complex and expensive processes involved in the provision of sterile solids having predetermined particle size ranges are avoided, and aseptic intrusions for sampling, sub-division, packaging and storage of a sterilized solid under sterile conditions are eliminated. Discoloration of sterile solids by dry heat sterilization is also eliminated.

WHAT WE CLAIM IS:—

1. A process for sterilizing particulate substantially water-insoluble solid medicinal material which comprises suspending the particulate solid medicinal material in a saturated aqueous solution of sodium chloride containing an excess of undissolved sodium chloride, heating the saturated sodium chloride solution containing the particulate medicinal material and excess of sodium chloride to an elevated temperature above 100°C, maintaining said elevated temperature until sterilization is effected, and then allowing the sterilized product to cool, the excess of sodium chloride being sufficient to maintain a saturated solution of it at the said elevated temperature.

2. A process according to claim 1, wherein the sodium chloride solution is heated under elevated pressure.

3. A process according to claim 1—2, wherein the sodium chloride solution is heated to a temperature of from 110—130°C.

4. A process according to claim 1, 2 or 3, wherein the excess of sodium chloride is 10% above the amount necessary to form a saturated solution at 100°C.

5. A process according to any one of the preceding claims, wherein the sodium chloride solution also contains sodium bisulfite.

6. A process according to any one of the preceding claims, wherein the sodium chloride solution also contains a wetting agent.

7. A process according to any one of the preceding claims, wherein the medicinal material is a non-electrolyte salt.

8. A process according to any one of the preceding claims, wherein the medicinal material is a steroid compound.

9. A process according to claim 8, wherein the medicinal material is dexamethasone or a derivative thereof.

10. A process according to claim 9, wherein the medicinal material is dexamethasone acetate or phosphate.

11. A process according to claim 1, substantially as hereinbefore described in any one of Examples 2—16.

12. Particulate medicinal material when sterilised by a process claimed in any one of the preceding claims.

13. A medicinal material comprising a suspension of a sterilised material according to claim 12 in a sterile aqueous medium.

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